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10/568,762

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EXAMINER

SWOPE, SHERIDAN

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|--------------------------------------|------------------------------------|--|
| Office Action Summary | Application No. 10/568,762 | Applicant(s) GOLZ ET AL. | |
| | Examiner SHERIDAN SWOPE | Art Unit 1652 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 09 October 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2,3 and 27-54 is/are pending in the application.
- 4a) Of the above claim(s) 27,28,33 and 34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2,3,29-32 and 35-54 is/are rejected.
- 7) ☒ Claim(s) 2,3,29-32 and 35-54 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1008</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicants' response of October 9, 2008, to the Office Action of July 9, 2008, is acknowledged. It is acknowledged that Claims 2, 30-32, and 36-38 have been amended and Claims 39-54 have been added. Claims 2, 3, and 27-54 are pending. Claims 27, 28, 33, and 34 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 2, 3, 29-32, and 35-54 are hereby examined.

Information Disclosure Statement

A reference of the Information Disclosure Statement filed October 9, 2008, as indicated by strike-out, has not been considered because it has not been filed. If Applicants wish for the reference to be considered, it should be filed with a supplementary Information Disclosure Statement.

Claims-Objections

Claims 2, 3, 29-32, and 35-54 are objected to for reciting non-elected subject matter. Applicants are reminded that their elected invention is directed to a method of screening **in vitro**, followed by screening in vivo.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 29-32, and 35-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

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Claims 2, 3, 29-32, and 35-51 are rendered indefinite because it is unclear how steps (i) and (ii) in Claims 2 and 3 contribute to the recited method of screening for therapeutic agents. For purposes of examination, it is assumed that the KLK8 activity detected in steps (i) and (ii) would be compared to determine if the test agent is a modulator of KLK8 protease activity and, if the test agent is a modulator, the test agent would be used in step (iii).

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Rejection of Claims 2, 3, 29-32, and 35-38 under 35 U.S.C. 112, first paragraph/enablement, for some of the same reasons explained in the prior action, is maintained. New Claims 39-54 are herein rejected under 35 U.S.C. 112, first paragraph for lack of enablement, for the same reasons. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(A) Claims 2 and 3 are amended to recite a genus of KLK8 polypeptides which “comprise an amino acid sequence which has at least 90% homology with the amino acid sequence SEQ ID NO:2”, which renders moot one basis of the rejection.

(B) The Action’s faulting the specification for not providing evidence that KLK8 causes or cures any specific disease is a red herring. This information is not required to enable the claimed screening methods. None of the methods recites or requires treatment or cure of a

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specific disease. KLK8 need not be the cause of a disease to be a useful target for treating a symptom of a disease.

These arguments are not found to be persuasive for the following reasons.

(A) This argument is not found to be persuasive. By use of “comprising” language, these claims encompass polypeptides, wherein the activity is not derived from the sequence homologous to SEQ ID NO: 2. The specification fails to enable the skilled artisan to make and use the full scope of said genus of polypeptides.

(B) MPEP 2111.02 states:

"If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim."

Claims 2 and 3 clearly recite “A method of screening for therapeutic agents useful in the treatment of a disease”. Thus, in the instant case, the preamble gives life and meaning to the claims; any agent identified as a KLK8 modulator must be able to be useful for treating a disease. Neither the specification nor the prior art provides an expectation that an agent identified as a KLK8 modulator will be useful for treating any cardiovascular, metabolic, urological, or reproductive diseases. Thus, the specification fails to enable the skilled artisan to make and use the full scope of the recited invention.

For these reasons and those explained in the prior action, rejection of Claims 2, 3, 29-32, and 35-54 are rejected under 35 U.S.C. 112, first paragraph for lack of enablement.

Written Description

Rejection of Claims 2, 3, 29-32, and 35-38 under 35 U.S.C. 112, first paragraph/written description, for some of the reasons explained in the prior action, is maintained. New Claims 39-

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54 are herein rejected under 35 U.S.C. 112, first paragraph/ written description, for the same reasons. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(C) Claims 2 and 3 are amended to recite a genus of KLK8 polypeptides which “comprise an amino acid sequence which has at least 90% homology with the amino acid sequence SEQ ID NO:2”, which renders moot one basis of the rejection.

(D) The specification discloses determining effects of test compounds on a symptom of diseases in in vivo assays (pg 42-43). In vivo model systems for the recited disorders were well known in the art.

These arguments are not found to be persuasive for the following reasons.

(C) This argument is not found to be persuasive. By use of “comprising” language, these claims encompass polypeptides, wherein the activity is not derived from the sequence homologous to SEQ ID NO: 2. The specification fails to describe any such polypeptides or the use thereof.

(D) As explained above, the preamble in Claims 2 and 3, reciting “A method of screening for therapeutic agents useful in the treatment of a disease”, gives life and meaning to the claims. Thus, any agent identified as a KLK8 modulator must be able to be useful for treating a disease. Neither the specification nor the prior art provides an expectation that an agent identified as a KLK8 modulator will be useful for treating any cardiovascular, metabolic, urological, or reproductive diseases. Thus, the recited invention in was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the full scope of the claimed invention.

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For these reasons and those explained in the prior action, rejection of Claims 2, 3, 29-32, and 35-54 are rejected under 35 U.S.C. 112, first paragraph/written description, is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 2, 3, 29, 30, 32, 35, 36, 38, 40, 45, and 49-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimizu et al, 1998 in view of Yoshida et al, 1998 and further in view of Shimizu-Okabe et al, 2001 and Small et al, 1998. Shimizu et al teach a method for identifying inhibitors of the isolated mouse KLK8 protein (Table II) including the use of [³H]DFP-labeled KLK8 protein in said assay (Fig 6). The skilled artisan would know that, using said inhibitors at high concentrations, for example 10mM leupeptin (Table 11), would displace a ligand previously bound at the same site. Shimizu et al do not teach a method for identifying inhibitors of the human KLK8 protein, as set forth by SEQ ID NO: 2 herein. Yoshida et al teach the human KLK8 protein, as set forth by SEQ ID NO: 2 herein. It would have been obvious to a person of ordinary skill in the art to use the protein of Yoshida et al in the method of Shimizu et al. It would also be obvious to use any identified modulator as a known regulator of human KLK8 as a control in subsequent assays. Motivation to do so derives from the desire to identify inhibitors of the human KLK8 protein. The expectation of success is high that, one or more of the assay systems used by Shimizu et al will be useful for assaying human KLK8 activity, since

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mouse and human KLK8 have 72% identity and human KLK8 is predicted to cleave at a P1 basic residue (Yoshida et al; pg 11, para 4).

Neither Shimizu et al, Yoshida et al, nor the combination thereof teaches determining the effect of an inhibitor of human KLK8 activity on a symptom of disease in vivo. Shimizu-Okabe et al teach that KLK8 is highly expressed in Alzheimer's disease hippocampus, which strongly suggested a pathological association (Fig 2; pg 2751, para 1). Thus, it would be obvious to a person of ordinary skill in the art to determine the effect of an inhibitor of human KLK8 activity on a symptom(s) of Alzheimer's disease. Said symptoms and methods for assessing said symptoms are described by Small et al. Therefore, Claims , 3, 29, 30, 32, 35, 36, 38, 40, 45, and 49-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimizu et al, 1998 in view of Yoshida et al, 1998 and further in view of Shimizu-Okabe et al, 2001 and Small et al, 1998.

Claims 31 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Shimizu et al, 1998, Yoshida et al, 1998, Shimizu-Okabe et al, 2001, and Small et al, 1998, in view of Piesecki et al, 1993. The teachings of the combination of Shimizu et al, Yoshida et al, Shimizu-Okabe et al, and Small et al are described above. Said combination does not teach using test agents that are coupled to a detectable label. However, the use of labeled molecules was well-known in the art. For example, Piesecki et al teach the making of His6-tag labeled proteins which can be used for essentially any purpose, including testing as a modulator in enzyme assays. It would have been obvious to a person of ordinary skill in the art to use the method of Piesecki et al to prepare His6- tagged test compounds to be used in the method rendered obvious by the combination of Shimizu et al, Yoshida et al, Shimizu-Okabe et al, and Small et al. Motivation to do so derives from the ease in purification of the His6-tag labeled

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compounds. The expectation of success is high, as the making and using of His6-tag labeled proteins was well-known in the art. Therefore, Claims 31 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Shimizu et al, 1998, Yoshida et al, 1998, Shimizu-Okabe et al, 2001, and Small et al, 1998, in view of Piesecki et al, 1993.

Allowable Subject Matter

No claims are allowable.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Any new references were cited solely to support rejections based on amendment or rebut Applicants' arguments. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

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Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that Applicants put the serial number on every page of their response.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-092834. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652